

SYMPOSIUM REVIEW

Activity-dependent synaptic plasticity of NMDA receptors

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Activity-dependent, bidirectional control of synaptic efficacy is thought to contribute to many forms of experience-dependent plasticity, including learning and memory. Although most excitatory synapses contain both AMPA and *N*-methyl-D-aspartate receptors (AMPA and NMDARs), most studies have focused on the plasticity of synaptic AMPARs, and on the pivotal role of NMDA receptors for its induction. Here we review evidence that synaptic NMDARs themselves are subject to long-term activity-dependent changes by mechanisms that may differ from that of synaptic AMPARs. The bidirectional modulation of NMDAR-mediated synaptic responses is likely to have important functional implications for NMDAR-dependent forms of synaptic plasticity.

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Introduction

In the central nervous system, activity-dependent bidirectional control of synaptic efficacy, as exemplified by various forms of long-term potentiation (LTP) and long-term depression (LTD), is thought to contribute to many forms of experience-dependent plasticity, including learning and memory (Malenka & Bear, 2004). At excitatory synapses, synaptic strength is regulated in great part by changes in the function and number of postsynaptic glutamate receptors, which include α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPA), *N*-methyl-D-aspartate receptors (NMDARs) and kainate receptors (Hollmann & Heinemann, 1994). Because AMPARs are the predominant ionotropic glutamate receptors mediating basal synaptic transmission, almost all work on the mechanisms underlying LTP and LTD has focused on the modulation of AMPAR-mediated synaptic responses. The prevailing view is that NMDARs play a pivotal role in the induction of many forms of activity-dependent LTP and LTD, by acting as a coincidence detector of presynaptic and postsynaptic firing (Malenka & Bear, 2004). This property depends both on the block of NMDA receptor channels by Mg^{2+} at resting membrane potential and on their high permeability to Ca^{2+} . An NMDA-mediated

rise in postsynaptic Ca^{2+} activates kinases, notably CAMKII, PKA, PKC and mitogen-activated protein kinase (MAPK), and protein phosphatases, which ultimately results in an increase or decrease of AMPAR density and/or conductance (Kerchner & Nicoll, 2008; Newpher & Ehlers, 2009). In the context of the function of NMDARs in synaptic plasticity and memory formation (Malenka & Bear, 2004; Nakazawa *et al.* 2004), a critical question is whether, like synaptic AMPARs, NMDARs

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undergo long-lasting modulation by synaptic activity. Once thought to be relatively stable at synapses, synaptic NMDARs are slowly emerging as subjects of intense plasticity and, like the AMPARs, in an activity-dependent manner. This review focuses on recent advances on the plasticity of synaptic NMDARs induced by synaptic activity.

Properties of NMDA receptors

NMDARs are heteromeric assemblies of NR1 (GluN1, with 8 different splice variants), NR2 (GluN2A, GluN2B, GluN2C and GluN2D) and NR3 (GluN3A and GluN3B) subunits that form ligand-gated channels with various cellular, biophysical and pharmacological properties depending on the composition of subunits and splice variants (Cull-Candy & Leszkiewicz, 2004; Paoletti & Neyton, 2007). The stoichiometry of NMDA receptors has not been firmly established, but the consensus is that they are most often tetramers composed of two NR1 subunits and two NR2 subunits (Paoletti & Neyton, 2007; Ulbrich & Isacoff, 2008). NMDA receptor subunits contain a long extracellular N-terminal domain, three true transmembrane segments, a re-entrant pore loop, and an intracellular C-terminal domain of variable length (Mayer, 2005). The C-terminus of both NR1 and NR2 subunits interacts with several intracellular scaffolding proteins, is subject to phosphorylation, and as such is involved in the regulation of receptor trafficking and function (Salter & Kalia, 2004; Lau & Zukin, 2007; Groc *et al.* 2009). Glutamate binds to the NR2 subunits while the co-agonist glycine binds to the NR1 subunit. The N-terminal domain of NR2 subunits is an important determinant for the functional properties of NMDARs. It is involved in the sensitivity to allosteric inhibitors like ifenprodil and zinc, as well as in the modulation of the open probability (Perin-Dureau *et al.* 2002; Hatton & Paoletti, 2005; Gielen *et al.* 2008). NR2 subunits are also critical for determining the high affinity for glutamate, modulation by glycine, sensitivity to voltage-dependent block by Mg^{2+} , fractional Ca^{2+} current and channel kinetics (Cull-Candy & Leszkiewicz, 2004; Paoletti & Neyton, 2007).

Synaptic NMDARs are localized in the post-synaptic density where they are structurally organized in a large macromolecular complex composed of scaffolding proteins and adaptors that physically link NMDARs to downstream signalling molecules, kinases and phosphatases, and to other transmembrane proteins such as adhesion proteins and mGluRs (Husi *et al.* 2000). Trafficking of NMDARs from the intracellular compartments to the synaptic and non-synaptic membrane has been extensively studied and reviewed recently (Chen & Roche, 2007; Lau & Zukin, 2007; Groc *et al.* 2009). Membrane export and synaptic insertion of NMDARs involves intrinsic trafficking signals specific for

each subunit and splice variant, and complex interactions between NMDARs and a variety of interacting proteins, including PDZ-domain proteins such as PSD-95 and SAP102. Membrane insertion and regulated endocytosis of NMDARs is also tightly controlled by phosphorylation (Chen & Roche, 2007; Lau & Zukin, 2007). Synaptic activity regulates the number and subunit composition of synaptic membrane receptors (Lau & Zukin, 2007). Despite the extensive literature on the regulation of cellular trafficking of NMDARs, our understanding of the molecular mechanisms underlying the insertion and retrieval of receptors in LTP or LTD of NMDARs lags well behind our current knowledge on the synaptic plasticity of AMPARs.

Modulation of NMDA receptor function

Because changes in the number, composition and/or function of NMDARs are expected to have important physiological and pathological consequences, there has been a wide interest in describing cell-signalling molecules capable of modulating synaptic NMDARs. Extracellularly, NMDARs can be modulated by glycine and D-serine, which act as co-agonists to potentiate NMDAR function (Johnson & Ascher, 1987; Oliet & Mothet, 2009). Extracellular zinc inhibits NMDAR function by binding to the N-terminal domain and by increasing proton inhibition (Paoletti *et al.* 2009). Polyamines and redox modulators have also been reported to influence NMDA receptor functions (Cull-Candy & Leszkiewicz, 2004).

The C-terminal domain of NMDAR subunits contains many serine/threonine phosphorylation sites, which are substrates for cAMP-dependent protein kinase A (PKA), protein kinase C (PKC), protein kinase B (PKB), CaMKII, cyclin-dependent kinase-5 (Cdk5) and casein kinase II (CKII) (Chen & Roche, 2007). For example, PKC and PKA activation increase NMDAR-mediated currents and Ca^{2+} permeability (Chen & Huang, 1992; Raman *et al.* 1996; Lu *et al.* 1999; Lan *et al.* 2001; Skeberdis *et al.* 2006). Phosphorylation by the Src family of protein tyrosine kinases (SFKs) upregulates NMDAR function. Activation of numerous G protein-coupled receptors, including M1 muscarinic receptors, LPA receptors, mGluR1 and mGluR5 and PACAP1 receptors, enhances NMDA receptor function via phosphorylation of the NMDA receptor channel (Salter & Kalia, 2004). Interestingly, the different G protein-coupled receptors seem to converge onto Src-family kinases which constitute a molecular hub for signalling pathways that enhance NMDAR activity (Salter & Kalia, 2004). All these studies have relied on the exogenous activation of NMDAR modulatory pathways. Therefore, the physiological conditions under which such modulations occur and their consequences on activity-dependent synaptic plasticity have mostly remained elusive.

LTP of synaptic NMDA receptors

There has been considerable debate whether LTP of AMPAR-mediated responses was accompanied by a long-lasting potentiation of synaptic NMDARs. Pharmacologically isolated NMDA receptor-mediated responses in CA1 were reported to undergo synapse-specific LTP in response to high frequency stimulation of Schaffer collaterals (Sch) (Bashir *et al.* 1991; Berretta *et al.* 1991) in parallel to LTP of AMPAR-mediated responses, although LTP of NMDAR-mediated responses requires a higher threshold for induction (Berretta *et al.* 1991; Aniksztejn & Ben-Ari, 1995). In CA1, LTP was initially seen as a predominant potentiation of the AMPA receptor-mediated component and followed by a delayed proportional potentiation of the NMDA component of the field EPSP, such that LTP did not affect the relative contribution of the two types of receptors (Xiao *et al.* 1995; see also Watt *et al.* 2004) at neocortical synapses. LTP of isolated NMDA-EPSCs in CA1 pyramidal cells was later observed and proposed to be of presynaptic origin (Kullmann *et al.* 1996). However, several other studies have found little or no LTP of NMDA-EPSCs under similar experimental conditions (Kauer *et al.* 1988; Muller & Lynch, 1988; Perkel & Nicoll, 1993; Liao *et al.* 1995; Durand *et al.* 1996; Heynen *et al.* 2000; Montgomery & Madison, 2002). The reason for these discrepancies is unclear, but likely to rely on the experimental conditions, especially intracellular Ca^{2+} buffering (see Harney *et al.* 2006), and possibly on the developmental stages of the animals.

LTP of NMDA-EPSCs also occurs in the dentate gyrus (O'Connor *et al.* 1994, 1995) (Fig. 1), at hippocampal mossy fibre synapses onto CA3 pyramidal cells (mf-CA3

synapses) (Kwon & Castillo, 2008; Rebola *et al.* 2008), and in ventral midbrain dopamine neurons (Harnett *et al.* 2009). Most of the earlier studies providing evidence for LTP of NMDA-mediated synaptic responses used protocols that also triggered LTP of the synaptic AMPA component. Recently, we and others have observed that a robust LTP of NMDA-EPSCs but not of AMPA-EPSCs was induced at mf-CA3 synapses with short bursts of stimuli (Kwon & Castillo, 2008; Rebola *et al.* 2008). This selective LTP of NMDA-EPSCs, induced with physiologically relevant patterns of stimulation, provides clear evidence that synaptic NMDARs can undergo activity-dependent long-term modifications with mechanisms different from the ones responsible for LTP of AMPARs.

Our understanding of the mechanisms of LTP of NMDA-EPSCs has recently progressed (Fig. 2) (Grosshans *et al.* 2002; Harney *et al.* 2006; Harney *et al.* 2008; Kwon & Castillo, 2008; Rebola *et al.* 2008; Harnett *et al.* 2009). These studies have converged on the notion that LTP of NMDA-EPSCs is expressed postsynaptically and requires an influx of postsynaptic Ca^{2+} consecutive to the activation of type I mGluRs and NMDARs (O'Connor *et al.* 1995; Harney *et al.* 2006; Kwon & Castillo, 2008; Rebola *et al.* 2008; Peng *et al.* 2009). In DA neurons, LTP requires release of Ca^{2+} from internal stores, whereas PKA activity gates LTP induction by regulating the magnitude of Ca^{2+} signal amplification (Harnett *et al.* 2009). At mf-CA3 synapses postsynaptic adenosine $\text{A}_{2\text{A}}$ receptors are essential for inducing LTP of NMDA-EPSCs (Rebola *et al.* 2008). $\text{A}_{2\text{A}}$ receptors may play a role in the amplification of Ca^{2+} signals, although their precise function in the induction LTP of NMDA-EPSCs is unknown. The expression mechanism is likely to involve insertion of NMDARs in the membrane

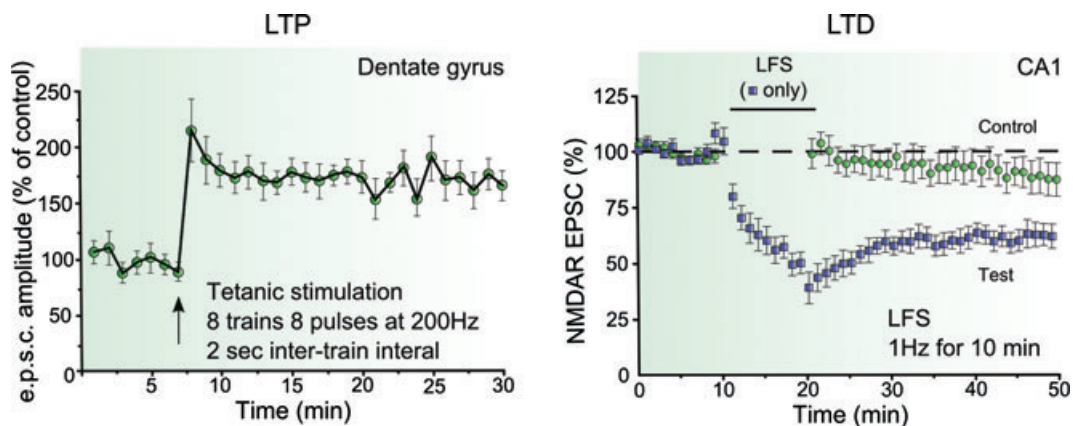


Figure 1. Examples of LTP and LTD of NMDARs

Tetanic stimulation consisting of eight trains each of eight pulses at 200 Hz, inter-train interval 2 s, applied under current clamp configuration at resting membrane potential during tetanus induces LTP of NMDA-EPSCs in dentate gyrus granule cells (reproduced from O'Connor *et al.* 1994 with permission from Nature Publishing Group). On the other hand, a 1 Hz stimulation for 10 min while holding the cells at -40 mV induces LTD of NMDA-EPSCs in CA1 area of the hippocampus (reproduced from Selig *et al.* 1995 with permission from Elsevier).

in a PKC- and Src-dependent process (Grosshans *et al.* 2002; Kwon & Castillo, 2008; Rebola *et al.* 2008), although long-lasting changes in the properties of existing synaptic NMDARs cannot be excluded. In the dentate gyrus, there is evidence for the recruitment of extrasynaptic NMDARs, in particular NR2D-containing NMDARs, during LTP of NMDA-EPSCs (Harney *et al.* 2008). In contrast, in DA neurons, LTP of NMDA-EPSCs is unlikely to be associated with changes in subunit composition (Harnett *et al.* 2009). Interestingly, in CA1 pyramidal cells, the subunit composition of synaptic NMDARs can quickly change in an activity-dependent manner at neonatal, but not mature, synapses (Bellone & Nicoll, 2007). The incorporation of NR2B subunit in synaptic NMDARs changes both the charge transfer and kinetics of synaptic NMDA EPSCs but not their amplitude (Bellone & Nicoll, 2007). However, it was recently reported that in 2- to 3-week-old rats, LTP of NMDA-EPSCs in CA1 pyramidal cells resulted from the membrane insertion of NR2A-containing receptors (Peng *et al.* 2009). Much further work is needed to understand the molecular mechanisms of LTP of NMDA-EPSCs.

LTD of synaptic NMDA receptors

In contrast to LTP, LTD of NMDAR-mediated synaptic responses has been consistently observed in response to induction protocols that elicit NMDAR-dependent LTD of AMPAR responses (Xie *et al.* 1992; Gean & Lin, 1993; Xiao *et al.* 1994; Selig *et al.* 1995; Montgomery & Madison, 2002) (Fig. 1). In the dentate gyrus the direction of plasticity of NMDAR following either high or low frequency stimulation appears to depend on intracellular free Ca^{2+} concentration in granule cells, with LTD being induced in conditions of high buffer capacity (Harney *et al.* 2006). LTD of NMDAR-mediated synaptic responses can be induced by specific patterns of afferent activity in CA1 pyramidal cells, through mechanisms apparently distinct from that underlying LTD of AMPAR-mediated responses (Selig *et al.* 1995; Morishita *et al.* 2005).

Unlike LTD of AMPA-EPSCs, which depends on dynamin-mediated receptor endocytosis, LTD of NMDA-EPSCs in CA1 pyramidal cells is unaffected by inhibitors of internalization (Morishita *et al.* 2005). Instead, the actin stabilizer phalloidin and a cofilin

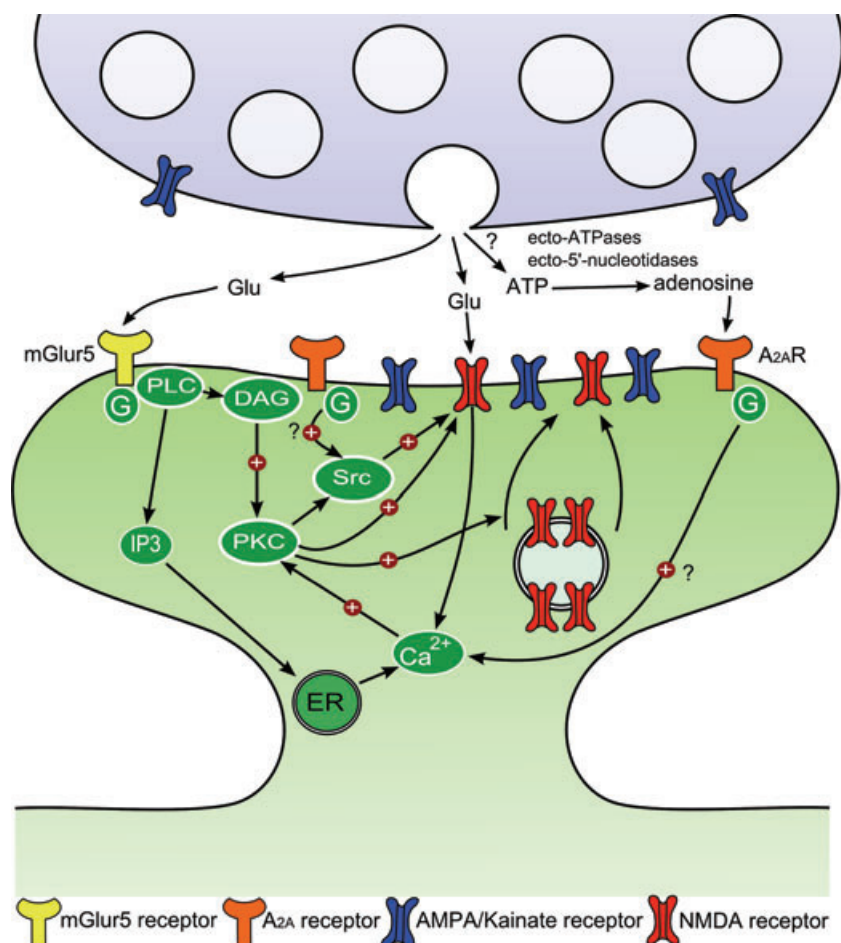


Figure 2. Schematic illustration of LTP of NMDARs at hippocampal mossy fibre synapses

Short bursts of stimulation of mossy fibres lead to the activation of NMDA, mGluR5 and adenosine $\text{A}_{2\text{A}}$ receptors that jointly induce LTP of NMDA-EPSCs in CA3 pyramidal neurons. mGluR5 couples to phospholipase C (PLC) via a G_q protein, which promotes the formation of inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 triggers Ca^{2+} release from intracellular stores, and both Ca^{2+} and DAG activate protein kinase C. Once activated, PKC can also activate Src kinases. PKC or Src may trigger the SNARE-dependent insertion of new NMDARs into the postsynaptic membrane. PKC or Src kinases can also enhance open probability of postsynaptic NMDARs, increasing postsynaptic Ca^{2+} rise and thus favouring LTP induction. The role of adenosine $\text{A}_{2\text{A}}$ receptors in LTP of NMDAR induction is not clear but could rely on an increase in postsynaptic Ca^{2+} rise through direct coupling of $\text{A}_{2\text{A}}$ receptors to the PLC pathway or on a potentiation of mGluR5 function. Additionally, activation of Src kinase by $\text{A}_{2\text{A}}$ receptors might also facilitate the induction of LTP of NMDA-EPSCs.

inhibitory peptide each block LTD of NMDAR-EPSCs, supporting a role for Ca^{2+} -dependent depolymerization of the actin cytoskeleton (Morishita *et al.* 2005). These studies thus propose a change in the function of synaptic NMDARs, consistent with studies reporting an activity-dependent inactivation of NMDAR channels (Rosenmund *et al.* 1995) by modulation of the actin cytoskeleton (Krupp *et al.* 1999). However, at synapses between CA3 connected pairs, LTD of NMDA-EPSCs is dynamin dependent and appears to involve NMDAR endocytosis (Montgomery & Madison, 2002; Montgomery *et al.* 2005). The role of mGluRs in LTD of NMDA-synaptic responses is also debated, with reports of either independence (Morishita *et al.* 2005) or dependence on group I mGluRs (Yi *et al.* 1995; Harney *et al.* 2006; Peng *et al.* 2009). The dependency of LTD on mGluRs is possibly associated with the endocytic events involved in the depression of NMDAR-mediated synaptic responses. Indeed, application of the group I mGluR agonist (RS)-3,5-dihydroxyphenylglycine (DHPG) induces a long lasting depression of NMDA-EPSCs at CA1 synapses as well as internalization of NMDARs in cultured hippocampal neurons (Snyder *et al.* 2001). In addition, LTD triggered in the hippocampus *in vivo* correlates with a decrease of both AMPARs and NMDARs in synaptoneurosomal biochemical fractions (Heynen *et al.* 2000).

Future directions

Like synaptic AMPARs, synaptic NMDARs can be bidirectionally modified by different patterns of synaptic activity. There is in addition a large wealth of evidence, not addressed here, that NMDARs are tightly regulated by experience during development. Our understanding of the mechanisms of activity-dependent synaptic plasticity of NMDA receptors is only starting to emerge. Historically, the topic has faced contradictory results and might have been overlooked in part due to the apparently modest extent of synaptic plasticity of NMDARs and the relatively higher induction threshold required for LTP. A series of recent studies have provided evidence that robust forms of LTP of synaptic NMDARs can be elicited by physiologically relevant patterns of presynaptic stimulation. It is expected that this should stimulate the field to investigate the mechanisms contributing to synaptic plasticity, and to provide links with our extensive knowledge on NMDAR protein complexes and molecular mechanisms of trafficking events to and from synaptic sites. Future studies should for instance explore the role of membrane-associated guanylate kinases (MAGUKs) and the possibility of a switch in subunit composition of synaptic NMDARs, as well as changes in important functional properties such as

Ca^{2+} permeability. A pioneering study using two-photon uncaging of glutamate observed that NMDARs can indeed undergo activity-dependent modulation of Ca^{2+} permeability (Sobczyk & Svoboda, 2007). The possibility that LTD corresponds to increased lateral mobility of NMDARs and LTP to immobilization and stabilization of existing receptors at synaptic sites should also be investigated (Groc *et al.* 2009).

Synaptic plasticity of NMDARs is particularly important because these receptors play a pivotal role in synaptic plasticity, such that changes in the strength of synaptic NMDARs are expected to critically influence the threshold for induction of AMPAR-mediated synaptic plasticity, as well as experience-dependent structural plasticity during the course of development. Given that NMDARs mediate a rise in postsynaptic Ca^{2+} , future studies are warranted to explore the consequences of synaptic plasticity of NMDA receptors for the activity of Ca^{2+} -dependent processes, ranging from the regulation of intrinsic excitability to gene expression, in physiological and pathological conditions.

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